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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,128	07/20/2005	Randall J. Lee	UCAL-253US1	6822

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,128	LEE ET AL.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-8,13,14,19-22,25 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-8,13,14,19-22,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment filed 12/22/2004 is acknowledged Claims 1, 6-8, 13, 14, 19-22, 25, 26 are pending in the application and under current examination.

Information Disclosure Statement

The information disclosure statement filed on April 21, 2005 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the listing of GenBank accession numbers in page 3 does not contain the date of the publication. It has been placed in the application file, but the information referred to therein has not been considered as to the merits.

If applicant decides to correct the deficiency, the submission should contain only the references that have not been considered.

Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Specification

The specification contains sequence disclosures (page 28) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in

37 CFR 1.821(a)(1) and (a)(2) but are not present in the Sequence Listing and identified in the specification by sequence identifier numbers. Applicant must provide sequence identifiers, a paper copy and a computer readable copy of the Sequence Listing and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). A full response to this Office Action must include a complete response to the requirement for a Sequence Listing.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6-8, 13, 14, 19-22, 25, 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the

art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

The claimed invention is directed to genetically modifying a fibroblast cell to express a connexin protein, and contacting the modified fibroblast cell with a myoblast cell so that to establish an electrical connection between the two cell types, whereby the recombinant fibroblast cell exhibits conductive characteristics similar to that of the myocardial cell.

In view of instant disclosure, the specification contemplates using various cells for cardiac tissue repair including fibroblast cells. However, the specification is completely silent with regard to the electrical conductive characteristics of fibroblast cells. In view of the state of the art, the skilled artisan considers fibroblast cells as electrically inert cell type, therefore, fibroblasts had been introduced to the heart tissue to block the conduction of the region (WO 03/094855, IDS). The levels of the skilled is such that it is a common consent that in order to use fibroblasts for cardiomyoplasty, one needs to first induce fibroblast cell *transdifferentiation* into myogeneic cells. For exemple, *Etzion et al.* (Circulation 2002;106-S:I-125-30) teaches transfecting fibroblast cells with adenoviral vector expressing MyoD to force myogenesis of fibroblast cells. Even so, the myogenic converted fibroblasts did not express connexin 43 (Cx43) *in vitro*, only at one month after transplantation, the authors reported a few myogenic-

converted fibroblasts cells stained positive for the gap junction protein Cx43 in a disorganized fashion. Apparently it was well known in the art that fibroblast cells could be exploited for their therapeutic potential in cardiac repair, but it is unpredictable and the specification fails to teach that expressing Cx43 would change the electrical conductive characteristics of the fibroblast cells. This unpredictability could be seen in a post-filing publication, where *Kizana et al.* (Circulation 2005;111:394-8) transfected dermal fibroblasts with both MyoD and Cx43. *Kizana et al.* states, "WE DEMONSTRATED FOR THE FIRST TIME THAT THE PHENOTYPE OF FIBROBLASTS CAN BE MODIFIED BY LENTIVIRUS VECTOR-MEDIATED GENE TRANSFER TO PRODUCE EXCITABLE CELLS CAPABLE OF ELECTRICAL COUPLING. MEMBRANE EXCITABILITY WAS ACQUIRED BY FORCING MYOGENESIS THROUGH EXPRESSION OF MYOD, A SKELETAL MYOGENIC DETERMINATION FACTOR, AND THE CAPACITY OF GJIC THROUGH EXPRESSION OF CONNEXIN43" (page 394, emphasis added). Here, the conductive characteristics of the fibroblasts are influenced by at least two important elements, membrane excitability and gap junctional intercellular communication. It was unknown and the specification fails to teach the Cx43-mediated GJIC alone would be sufficient to make fibroblasts electrically active or whether such modification could alter the conductive characteristics to the extent similar to that of the myocardial cells, and thus the specification fails to provide an enabling disclosure for what is now claimed.

Given the broadest reasonable interpretation, the claims read on treating a cardiac conduction disturbance disease in humans by implanting genetically modifying fibroblast cells to express Cx43. With respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph entails the determination of what the claims recite and what the claims mean as a whole. As such, the claims clearly or implicitly state the intended

therapeutic use of the method, thus, the broadest reasonable interpretation of the claimed invention properly encompasses *ex vivo* gene therapy for disease treatment including prevention, alleviating and curing a disease, particularly cardiac conduction disturbance caused by any cardiac disorders, therefore, the claims will be evaluated by that standard.

The specification teaches injecting to heart tissue (AV node) of immunodeficient rats *myoblast* cells transduced with Cx43, which significantly improved electrical connection as measured by surface ECG PR intervals, AV nodal block cycle length, and AVN effective refractory period (example 6). The specification contemplates transplanting autologous Cx43-expressing cells in patients with a previous myocardial infarction (example 7). However, the specification fails to teach the electrical conductivity of Cx43-expressing fibroblast cells, the degree of improvement if any, and whether such electrical improvement has reached a therapeutic level so that any conduction disturbance could be effectively treated. The specification fails to disclose any data from the contemplated fibroblast cells, and fails to teach whether a Cx43 modified fibroblast cell is capable of bring about improved electrical connection, if so, whether it was sufficient to the level of treating a clinical cardiac conduction disturbance in any subject. Thus, it is necessary to evaluate the state of the art at the time of instant filing date.

Given the broadest reasonable interpretation, the claims read on treating a cardiac conductive disturbance in humans by implanting Cx43-modified fibroblast cells to establish electrically conduction similar to that of myocardial cells. However, since

fibroblasts was known to be electrically inert, the specification fails to teach that such is feasible. In view of the state of the art, even with the forced myogenesis, *Kizana et al.* teaches, "THE POSSIBILITY EXISTS THAT SOME CELLS ACQUIRE THE CAPACITY FOR GJIC WITHOUT BEING EXCITABLE. IN THIS SITUATION, THESE CELLS COULD ACT AS A CURRENT SINK AND RETARD IMPOULSE PROPAGATION" (column 2, page 397). This is likely to be the case for instantly claimed method since the Cx43-modified fibroblasts has not undergone forced myogenesis, and thus lacking excitability. *Kizana et al.* teaches that further investigation needs to be done for assessing the simultaneous effects of the acquisition of excitability and GJIC on electrical propagation. *Kizana et al.* also discusses the observation that the myogenic converted fibroblasts have reduced excitability compared to myocytes, and the possible clinical indication of this phenomenon (e.g. pages 397-8), and teaches, "THE FUNCTIONAL CONSEQUENCE OF JUXTAPOSITION OF CELLS WITH DISCREPANT ELECTROPHYSIOLOGICAL PROPERTIES REMAINS POORLY UNDERSTOOD. ACCORDINGLY, ONE OF THE CHALLENGES OF DEVELOPING SAFE AND EFFECTIVE GENE-BASED STRATEGIES FOR CONDUCTION REPAIR WILL BE DEFINING AND CONTROLLING BOUNDARY EFFECTS LIKELY TO SURROUND REGIONS OF GENE MODIFIED CELLS...THE JUXTAPOSITION OF SUCH CELLS COULD THEREFORE PROVIDE A POTENTIAL SUBSTRATE FOR FUNCTIONAL REENTRY AND THE GENERATION OF ARRHYTHMIAS". Clearly, since the Cx43 modified fibroblasts as currently claimed are unlikely to acquire a conductive characteristic similar to that of myocardial cells, and thus highly likely to cause arrhythmias rather than treating it, the claimed invention does not appear to be enabled in the absence of evidence to the contrary.

Further considerations with regard to therapeutic regimen of cardiac repair, *Murry et al* (J Cardiac Failure 2002;8:S532-41, IDS) teach muscle cell grafting has become a

promising alternative for treating heart failure due to heart infarction. However, the obstacle of transplantation with fetal and neonatal cardiomocytes is limited by graft cell death due to the ischemic injury. While fibroblast cells have good proliferation potential, one major challenge of using such for myocardial repair is getting sufficient graft cell mass without risking a tumor-like overgrowth, which prevent the practical use in human patients (e.g. abstract and paragraph bridging pages S537-8). *Reinecke et al* (Cardiovasc Pathol 2000;9:337-44, IDS) teach, "EXCESS PROLIFERATION, HOWEVER, CAN CAUSE GRAFTS TO EXPAND THE VENTRICULAR WALL AND POSSIBLY IMPAIR PUMP FUNCTION" (abstract). With regard to functional recovery, *Murry et al* reviewed several studies at the time and concluded, the experimental studies have shown that skeletal myoblast grafting results in improved global contractile function mainly because it significantly attenuates ventricular remodeling after an infarct (page S538). Apparently, the conduction disturbance could occur due to a number of reasons, from the defect in conduction tissue to scar tissue formation. The skeletal muscle cells may improve heart contractile function, there is no evidence that fibroblast cells could do so. Neither the specification nor the art of record show any heart conduction disturbance could be alleviated by supplementing fibroblast cells overexpressing Cx43, particularly in humans. *Murry et al* concluded at the post-filing date, "ALTHOUGH PROMISING EXPERIMENTAL LEADS ARE PRESENT, IT WILL TAKE A CONSIDERABLE AMOUNT OF CAREFUL, BASIC RESEARCH BEFOR THE PROMISE OF CELL THERAPY CAN BE REDUCED TO A CLINICAL PRACTICE" (column 1, page S540). In view of such, the invention does not appear to be enabled commensurate to the full scope of the claims in the absence of clarification of the contradictory evidence

found in the references. The specification fails to teach how to overcome the aforementioned difficulties in the art. It would have required undue experimentation for the skilled artisan intending to practice the instant invention.

Given the broadest reasonable interpretation, the claims encompass using connexins other than Cx43. However, the specification and the art of record are silent concerning the association of cardiac cells and role of other type of connexin, and only the Cx43 is known to be predominant in cardiac cells. Accordingly, the specification fails to support the full scope of the claims.

Given the broadest reasonable interpretation, the claims encompass administering Cx43-modified cells to the heart (so they could contact the myocardial cells) via any route of administration. However, the specification and the art of record only teach the cardiac vascular infusion or direct injection. The record is silent concerning the outcome of the modified cells when administered from a site remote from the heart, how they could reach the site of cardiac infarction in sufficient amount so that a therapeutic effect could be asserted. Accordingly, the specification fails to support the full scope of the claims.

Given the broadest reasonable interpretation, the claims encompass using allogenic or xenogenic cells for transplantation. However, the art of record consistently teach using autologous cells to prevent an immune response, which may exacerbate the already ischemic heart tissue (e.g. *Kizana et al.* column 1, page 398). The specification fails to teach otherwise, and thus the specification fails to support the full scope of the claims.

In view of the nature and the breadth of these claims, they are gene therapy methods for cell transplants in humans. In view of the state of the art and the level of the skill, *Orkin et al.* (NIH Report, 1995 Dec) reviews the infant state of the art of gene therapy from before the instant invention was made. The overall conclusions were: 1) gene therapy for each disease would present its own scientific and clinical challenges; 2) no successful gene therapy protocol was known; 3) significant problems remained in all aspects of gene therapy, especially with respect to effective expression vectors; 4) one cannot predictably extrapolate the result of one animal model, such as mouse, to treatment of a disease in a different animal, such as human; and 6) assessment of known gene therapy protocols was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor definition of biochemical or disease endpoints (pages 1-2). Although the significant advance has achieved in the art, the general status of gene therapy art has not significantly changed. *Peterson* (STATEMENT OF AMY PATTERSON M.D., February 2000) reviews "THE SUCCESS OF THIS TECHNOLOGY [GENE THERAPY] IS DEPENDENT UPON NOT ONLY THE DELIVERY OF GENETIC MATERIAL INTO THE TARGET CELLS, BUT ALSO THE EXPRESSION OF THE GENE ONCE IT REACHES ITS TARGET SITE. BOTH OF THESE REQUIREMENTS POSE CONSIDERABLE TECHNICAL CHALLENGES". *Peterson* further teaches that out of 372 clinical trials registered with the NIH, only one percent of the trials (3) have progressed to Phase III efficacy studies. "FOR THIS REASON, IT IS PERHAPS MORE ACCURATE TO REFER TO THIS TECHNOLOGY AS 'GENE TRANSFER', RATHER THAN 'GENE THERAPY', UNTIL THERE IS MORE EVIDENCE FOR THE THERAPEUTIC BENEFIT OF THIS TECHNOLOGY". Since *ex vivo* gene therapy has not become a routine in the art, since the specification fails to provide a specific enabling

disclosure to guide the practice of the claim invention, it would have require undue experimentation for the skilled intending to practice instantly claimed invention.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is now claimed.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Applicant is advised that should claims 6 and 19 be found allowable, claims 13 and 22 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after

allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claims 1, 6-8, 13, 14, 19-22, 25, 26 of this application conflict with claims of Application No. 11/635,810. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is **(866) 217-9197**. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

Q. JANICE LI, M.D.
PRIMARY EXAMINER

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
April 30, 2007